REMARKS

Personal Interview

Applicants would like to express appreciation to Examiner Huynh and Examiner Chan for the courtesy extended to coinventor Dr. Erwin Gelfand and Applicants' agent Dr. Angela Sebor during the personal interview at the United States Patent Office on April 18, 2005. During the interview, the outstanding rejections under 35 U.S.C. § 102(b), 35 U.S.C. § 103 and 35 U.S.C. § 112, first paragraph were discussed. During the interview, Dr. Gelfand and Dr. Sebor reviewed the cited publication of Cadieux et al. (*Am. J. Respir Crit. Care Med.* 159:235-243, 1999) and Applicants' arguments regarding why this publication does not teach or suggest the claimed invention. The Examiner appeared to accept Applicants' arguments and agreed to reconsider the rejections. With regard to the enablement issues, the Examiner and Applicants discussed limiting the claims to the use of the CGRP peptide and removing the recitation of homologues and fragments thereof. Examiner Chan indicated that she would look into the issue of whether a sequence for CGRP should be provided in the claims or specification. Examiner Huynh also suggested that the independent claims be amended to remove the phrase ", or is at risk of developing," to avoid further issues with clarity. Finally, Examiner Huynh indicated that Claim 46 should be amended to clarify that the "provoking agent" be limited to "methacholine".

On April 21, 2005, Examiner Chan left a detailed telephone message for Angela Sebor regarding the issue of CGRP sequence. Examiner Chan stated that if the claim was limited to the intact peptide and reference to homologues and fragments were removed, this would be acceptable. Examiner Chan indicated that she had conferred with another Examiner and that it would not be necessary to introduce the sequence into the specification or claims.

Claim Amendments

Applicants have amended the claims as discussed with the Examiners on April 18. These amendments adopt the Examiner's suggestions as discussed on April 18 and involve either the cancellation of claims, comply with a requirement of form as discussed with the Examiner on April

18, or place the claims in a better condition for consideration on appeal, and therefore, Applicants respectfully request that the claim amendments be entered.

Objection to the Specification and Rejection of Claims 1, 3-10, 12-14, 20-30, 38-40 and 42-47 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1, 3-10, 12-14, 20-30, 38-40 and 42-47 under 35 U.S.C. § 112, first paragraph, on the basis of enablement, largely for the reasons of record.

Without any intent to prejudice or disclaim the subject matter of the prior claims, Applicants have adopted the Examiners' suggestion and have limited the claims to calcitonin gene related peptide (CGRP), which is believed to largely obviate the Examiner's concerns in this rejection. Additionally, dependent Claims 27, 28, 38-40, 42, 45 and 47 have been cancelled without prejudice to or disclaimer of the subject matter therein, which further obviates additional portions of the Examiner's rejection. It is again noted that in a telephone message to Angela Sebor on April 21, Examiner Chan indicated that limitation of the claims to the CGRP peptide would be acceptable, and that Applicants would not need to recite a sequence for CGRP in the claims or specification.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-10, 12-14, 20-30, 38-40 and 42-47 under 35 U.S.C. § 112, first paragraph.

Objection to the Specification and Rejection of Claims 46 and 47 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 46 and 47 under 35 U.S.C. § 112, first paragraph, on the basis of new matter.

As suggested by the Examiner on April 18, Claim 46 has been amended to recite that the "provoking agent" is methacholine. This amendment is supported on page 13-14 of the specification. Claim 47 has been cancelled without prejudice or disclaimer of the subject matter therein.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 46 and 47 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38, 42-43 and 45-47 Under 35 U.S.C. § 102(b):

The Examiner has maintained the rejection of Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38, 42-43 and 45-47 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Cadieux et al. The Examiner contends that Cadieux et al. teach a method of inhibiting allergen-induced airway hyperresponsiveness (AHR) by administering CGRP, referring to Figure 2 of Cadieux et al., for example. The Examiner contends that at the highest dose of CGRP (Table 1 of Cadieux et al.), CGRP inhibits AHR to substance P (SP) in ovalbumin-sensitized guinea pigs (7.2 $\pm$ 4.5) as compared to the control (20.3 $\pm$ 1.5). The Examiner also asserts that the recitation of a provoking agent that causes a 20% fall in FEV1(PC_{20}FEV1) wherein the concentration is less than the concentration required to cause a 20% fall in FEV1(PC_{20}FEV1) in non-allergen sensitized animals is within the purview of Cadieux et al.

Applicants again traverse the rejection of Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38, 42-43 and 45-47 under 35 U.S.C. § 102(b). Applicants submit that Cadieux et al. fail to teach that the administration of CGRP to a mammal that has been sensitized to an allergen inhibits allergen-induced airway hyperresponsiveness in the mammal. Applicants refer to the prior responses of record and elaborate on the rebuttal of the rejection as follows.

As discussed in the April 18 interview, Applicants respectfully submit that the Examiner appears to be misinterpreting the results presented by Cadieux et al., as summarized in the following points that were made by Dr. Gelfand and Dr. Sebor during the April 18 interview. First, if one looks at the experimental design used in the present specification, an effect of CGRP on airway hyperresponsiveness that results from *allergen-sensitization*, and not airway hyperresponsiveness that occurs in the absence of allergen-sensitization, is clearly demonstrated. Referring to Figs. 3A and 3B of the specification, for example, one can see that non-allergen-sensitized animals (i.e., the negative control; SAL) that have not been treated with CGRP have a baseline level of airway

resistance and dynamic compliance as a result of exposure to the provoking agent (methacholine) that is only a marginal increase in airway hyperresponsiveness as compared to in the absence of the provoking agent. In contrast, animals that are allergen-sensitized and have not been treated with CGRP (i.e., the positive control; OVA) have a marked increase in airway resistance and a marked decrease in dynamic compliance in a dose-dependent manner in response to challenge with the provoking agent. Therefore, this experiment specifically measures the effects of the administration of CGRP on *allergen-induced* AHR because there is a distinct positive and negative baseline that results from the allergen-sensitization. In Figs. 3A and 3B, the administration of CGRP to the allergen-sensitized animals (CGRP) resulted in a substantially complete inhibition of AHR as compared to in the absence of the CGRP (*i.e.,* one can clearly see that the CGRP-treated, allergen-sensitized animals had an airway response that is similar to a non-allergen-sensitized animal, which shows that CGRP had an effect on allergen-induced AHR).

In contrast, the experiments of Cadieux et al. are directed to the use of substance P (SP) to induce airway hyperresponsiveness in a mammal, which is an agent that potently and equally induces bronchoconstriction in both *non-sensitized* and allergen-sensitized animals, and therefore is not useful for distinguishing between other effects on the animals, such as allergen sensitization. Indeed, Cadieux et al. state that animals *were selected* to have the **same** response to SP, regardless of the OA-treatment (see Cadieux et al., page 236, col. 2, first full paragraph). Therefore, the experimental model of Cadieux et al. does not measure the effect of any agent on allergen-induced AHR, because the animals develop AHR **in response to SP** *regardless* of the allergen-sensitization state of the animal (*i.e.,* there is no difference in the AHR induced in an allergen-sensitized animal versus a non-allergen-sensitized control animal in the presence of the provoking agent). As a result of this experimental design to measure SP-induced AHR, to be able to measure any additional positive effect that might be a result of allergen-sensitization (which is still not a direct measure of CGRP on allergen-induced AHR), one would at a minimum have to see an effect in CGRP-treated, allergen-sensitized animals that is *better* than the effect on the CGRP-treated, non-sensitized control.

Referring to Table 1 of Cadieux et al., which is discussed by the Examiner, the control animals, when administered CGRP, showed a 20.3% inhibition in airway response in the bronchus

and a 47.3% inhibition in airway response in the parenchyma. However, the allergen-sensitized animals, when administered CGRP, showed only a 7.2% inhibition in airway response in the bronchus and a 18.7% inhibition in the parenchyma, which is substantially worse than the *control*! Therefore, as discussed above, the only type of AHR that can be measured in this experiment is the effect of CGRP on SP-induced AHR, not allergen-induced AHR, and the results specifically show that the effect of allergen-sensitization was to *worsen* the ability of CGRP to inhibit this SP-induced AHR. This is exactly what is concluded by Cadieux et al., as has been discussed in prior responses. Table 1 of Cadieux et al. shows that allergen-sensitization works against the ability of CGRP to inhibit *SP-induced AHR*, which is the opposite of a showing that CGRP actually inhibits allergen-induced AHR. With regard to Fig. 2 of Cadieux et al., this figure clearly shows that administration of CGRP to OA-sensitized animals resulted in **no** statistically significant inhibition of SP-induced AHR (see figure legend with regard to "Asterisks"). From this result, one can conclude that allergen-sensitization appears to have *prevented* CGRP from inhibiting *SP-induced* AHR. This teaches nothing about the effects of CGRP on allergen-induced AHR and if anything, suggests that allergen-sensitization has an inhibitory effect on the action of CGRP, which is also concluded by Cadieux et al. (see Discussion and prior responses).

Therefore, Cadieux et al. simply can not and do not teach any effect of CGRP on *allergen-induced* AHR. Moreover, Cadieux et al. teach that there was no improvement in SP-induced AHR in allergen-sensitized animals treated with CGRP as compared to controls, and in fact, Cadieux et al. teach that allergen-sensitization *inhibits* the ability of CGRP to reduce SP-induced AHR.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38, 42-43 and 45-47 under 35 U.S.C. § 102(b).

Rejection of Claims 1, 6-7, 10, 22, 24, 27, 30 and 40 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 6-7, 10, 22, 24, 27, 30 and 40 under 35 U.S.C. § 103, contending that these claims are unpatentable over Cadieux et al. in view of U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478, for the reasons of record.

Applicants again traverse the rejection under 35 U.S.C. § 103. Initially, Applicants refer to the discussion above with regard to Cadieux et al. and submit that, for these reasons, Cadieux et al. do not teach or suggest the presently claimed invention. Moreover, Applicants submit that the combination of Cadieux et al. with one or both of the '978 patent or the '478 patent do not remedy the deficiencies of Cadieux et al. alone, for the reasons of record (see, for Example, the response filed October 21, 2004). Furthermore, given that Cadieux et al. do not teach or suggest that administration of CGRP can inhibit allergen-induced AHR and moreover, given that Cadieux et al. clearly teach that in an inflammatory condition such as allergen-sensitivity, the ability of CGRP to impact SP-induced bronchoconstriction is severely impaired, one would be *dissuaded*, and certainly not motivated to combine the references as the Examiner has done. Furthermore, the negative results of Cadieux et al. would not provide one of skill in the art with any expectation of success, even in combination with the teachings of the cited patents.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 6-7, 10, 22, 24, 27, 30 and 40 under 35 U.S.C. § 103.

Rejection of Claims 1, 25 and 27 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 25 and 27 under 35 U.S.C. § 103, contending that these claims are unpatentable over Cadieux et al. in view of Suissa et al., for the reasons of record.

Applicants traverse the rejection of Claims 1, 25 and 27 under 35 U.S.C. § 103. Again, Applicants refer to the discussion of Cadieux et al. above and submit that, for these reasons, Cadieux et al. do not teach or suggest the presently claimed invention. Moreover, Applicants submit that the combination of Cadieux et al. with Suissa et al. does not teach or suggest the present invention, as the teachings of Suissa et al. do not make up for the deficiencies of Cadieux et al., as discussed previously (see, for Example, the response filed October 21, 2004).

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 25 and 27 under 35 U.S.C. § 103.

Rejection of Claims 1 and 27 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1 and 27 under 35 U.S.C. § 103, contending that these claims are unpatentable over Cadieux et al. in view of Drazen et al. or Abraham et al., or Abdelaziz et al., or Barnes et al. or Hoshino et al., for the reasons of record.

Applicants traverse the rejection of Claims 1 and 27 under 35 U.S.C. § 103. Applicants refer to the discussion of Cadieux et al. above and submit that, for these reasons, Cadieux et al. do not teach or suggest the presently claimed invention. Moreover, Applicants submit that the combination of Cadieux et al. with any of the above-identified secondary references does not teach or suggest the present invention, as discussed previously (see, for Example, the response filed October 21, 2004).

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1 and 27 under 35 U.S.C. § 103.

Rejection of Claims 1, 28 and 29 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 28 and 29 under 35 U.S.C. § 103, contending that these claims are unpatentable over Cadieux et al. in view of WO 98/03534, for the reasons of record.

Applicants traverse the rejection of Claims 1, 28, and 29 under 35 U.S.C. § 103. Applicants refer to the discussion of Cadieux et al. above and submit that, for these reasons, Cadieux et al. do not teach or suggest the presently claimed invention. For the reasons of record, Applicants assert that CGRP-RCF is not CGRP or an agonist or antagonist thereof. In any event, WO 98/03534 does not teach or suggest the use of CGRP or any compound to inhibit allergen-induced AHR and can not remedy the deficiencies of Cadieux et al. as discussed previously (see, for Example, the response filed October 21, 2004), nor is there any motivation or expectation of success provided by the combination, because even with WO 98/03534, Cadieux et al. clearly *dissuades* one from using CGRP to treat AHR during inflammatory conditions.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 28, and 29 under 35 U.S.C. § 103.

Applicants have attempted to respond to all of the issues raised in the January 25 Office Action and submit that the claims are in a condition for allowance. In the event that the Examiner

has any remaining concerns regarding the claims, the Examiner is encouraged to contact the below-named agent at (303) 863-9700 to expedite prosecution.

Respectfully submitted,

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